ADRENAL INCIDENTALOMA, BREAST CANCER AND UNRECOGNIZED MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

S.H. Kim^{1,*}, J.H. Park²

¹*Presbyterian Medical Center - Department of Internal Medicine*, ²*Jeonbuk National University Medical School - Department of Internal Medicine, Jeonju, Republic of Korea*

Abstract

Background. The incidence of adrenal incidentaloma has been increasing proportional to the use of radiologic examination. Multiple endocrine neoplasia (MEN1) syndrome may present with various tumors. The present study reports a case of adrenal incidentaloma with unrecognized MEN1 syndrome associated with breast cancer.

Clinical case. A 48-year-old woman presented with a 2.4cm left adrenal incidentaloma on abdominal computed tomography. Her history revealed primary amenorrhea, recurrent peptic ulcer and nephrolithiasis. Laboratory and radiologic examination revealed two pancreatic tail mass lesions with markedly elevated gastrin levels (1462 pg/mL), hypercalcemia with increased parathyroid hormone levels (72 pg/mL), a 1.5cm pituitary mass with hyperprolactinemia (234 ng/mL), a 1.0cm meningioma and a nonfunctional left adrenal mass. During this image work up, a 0.6cm nodule in the right breast was incidentally detected. Surgeries (laparoscopic distal pancreatectomy, parathyroidectomy and wide local excision of breast) and pathologic findings confirmed pancreatic neuroendocrine tumors, parathyroid gland hyperplasia, and breast cancer. Carbergoline treatment for 12 months decreased prolactin levels to 27 ng/mL. Genetic testing using peripheral blood revealed a pathogenic variant in MEN1 on chr11q13 (NM_000244.3:c.1365+1_1365+11 del, GTGAGGGACAG, heterozygous).

Conclusion. Considering the increasing incidence of adrenal incidentaloma and 20% prevalence of adrenal tumors in patients with MEN1, it is important to rule out MEN1 association in patients with adrenal incidentaloma. Additionally, breast cancer was detected during MEN1 work-up in this case. Female patients with MEN1 are at increased risk for breast cancer. Therefore, intensified breast cancer screening at a relatively young age should be considered in female MEN1 patients.

Key words: Adrenal incidentaloma, Breast cancer, Multiple endocrine neoplasia 1.

INTRODUCTION

Adrenal masses, often discovered incidentally, are termed adrenal incidentaloma. The incidence of adrenal incidentaloma has been increasing proportional to use of radiologic examinations such as computed tomography (CT), and their prevalence ranges from 0.4% to 5.0% (1). Adrenal lesions can be related to various diseases including multiple endocrine neoplasia 1 (MEN1). MEN, which can be hereditary or sporadic, can affect various endocrine/non-endocrine glands (2, 3). Frequent manifestations of MEN 1 are primary hyperparathyroidism, pancreatic endocrine tumors, and pituitary adenomas. Adrenal abnormalities related to MEN1 have been reported since before 1960 (3, 4). This disease can have ambiguous symptoms (2) and therefore, a considerable number of patients have had the disease without fully knowing their disease status (2). Nonfamilial sporadic forms may have developed in 8%-14% of patients with MEN1, and many patients do not know that they have the disease (2). Furthermore, a study performed in the Dutch MEN1 cohort was recently reported that women with MEN1 were likely to be diagnosed with breast cancer earlier than the reference population (median age, 45 years vs. 61.2 years) and recommended surveillance starting at age 40 for all women with MEN1 (5, 6). We herein reported a case of adrenal incidentaloma with unrecognized MEN1 syndrome associated with breast cancer, in a 48-year-old woman.

CASE REPORT

A 48-year-old woman presented to our hospital due to the discovery of an adrenal incidentaloma on a computed tomography (CT) scan performed at another hospital. The CT scan showed a 2.4-cm left adrenal mass with a peripheral-rim like enhancement on the contrast-

*Correspondence to: Ji Hyun Park MD, PhD, Jeonbuk National University Medical School, Division of Endocrinology and Metabolism, Department of Internal Medicine, 20 Geonji-ro, Deokjin-gu, Jeonju, 54907, Republic of Korea, E-mail: parkjh@jbnu.ac.kr

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enhanced image. While visiting our hospital, she had a normal blood pressure (114/68 mmHg) and heart rate (93 beats/min). She had no history of HTN. The patient was 156-cm tall and weighed 62 kg, with a BMI of 25.5 kg/m². There was no palpable mass on her neck or breast examination, and no abnormalities on extra-genitalia areas were observed. Her history revealed that she had primary amenorrhea but surprisingly she had not been to a clinic for reproductive axis evaluation. She had been intermittently taking a proton-pump inhibitor, omeprazole, for the last 10 years because of a recurrent peptic ulcer. A history of three rounds of extracorporeal shock wave lithotripsy treatment for nephrolithiasis was also identified. In her family history, her father died due to hepatocellular cancer at age 62. She had one sister aged 53 years and two brothers aged 51 and 47 years, respectively. None of her surviving family members had a history of tumors but her mother had hypertension.

Laboratory studies indicated the following: calcium 11.5 mg/dL (normal: 8.4-10.2), phosphorus 3.3 mg/dL (normal: 2.5-4.5), parathyroid hormone 72.8 pg/mL (normal: 15-65), 25OH-vitamin D 21.2 ng/mL, prolactin 234.8 ng/mL (4.79-23.3), FSH 0.6 mIU/mL (1.4-18.1), LH 0.07 mIU/mL (1.5-9.3), estradiol 49.24 pg/mL (middle follicular phase 30-139, middle luteal phase 54-242, and postmenopausal 15-75), free T4 18.6 pmol/L (11.5-23), TSH 1.44 mIU/L (0.17-4.05), IGF 1 189 ng/mL (87-267), plasma metanephrine 0.12 mg/mL (normal: <0.5), plasma normetanephrine 0.65 pg/mL (normal: <0.9), aldosterone 22.9 ng/dL, renin 1.34 ng/mL/h, testosterone 0.08 ng/mL (normal <0.95), DHEAS 143 µg/dL (30-333). Morning serum cortisol was 20.5 µg/dL, ACTH was 58 pg/mL (10-90), and overnight dexamethasone suppressed cortisol level was 1.0 µg/dL (normal: <1.8). Plasma gastrin level was 1462 pg/mL (normal <110).

Abdominal magnetic resonance image (MRI) identified a benign appearing multilocular cystic left adrenal mass (2.4cm), a pancreas tail mass (2.2cm), and hypertrophic gastropathy (Fig. 1). Sellar MRI identified a pituitary adenoma (1.5cm) and meningioma (1 cm) in the left tentorium cerebella (Fig. 2). Neck ultrasonography (US) did not identify any abnormalities in the thyroid and parathyroid glands. A Tc-99m MIBI parathyroid SPECT/CT showed increased MIBI uptake in the posterior portion of the right thyroid gland suggesting right parathyroid gland hyperplasia. In addition, a 0.6-cm breast nodule in the right upper quadrant was incidentally detected in the CT scan acquired during parathyroid SPECT/CT. A breast US and mammography identified a 5×7-mm indeterminate mass in the right breast, which correlated with the SPECT/CT findings. Core needle biopsy was performed at this lesion and the pathology indicated a ductal carcinoma *in situ*.

For the genetic study, informed consent was obtained from the patient, and a peripheral blood sample was collected. Genomic DNA was extracted using a Wizard Genomic DNA Purification Kit (Promega, Madison, WI, USA). Direct sequencing was performed using an ABI Prism 3130 genetic analyzer. A variant was detected at chr11q13 (MEN1 NM_000244.3:c.1365+1_1365+11 del, GTGAGGGACAG, heterozygous). This transcript variant occurring within the intron has been previously reported in association with MEN 1. (7) It has also been reported as c.1452del11 by Teh *et al.* (8). This variant is listed as pathogenic in ClinVar (Variation ID: 201001, <https://www.ncbi.nlm.nih.gov/clinvar/variation/201001/>).

Based on these findings, the patient was diagnosed with MEN1, which included pancreas neuroendocrine tumor (gastrinoma) in the pancreatic

Figure 1. Magnetic resonance image (a), (b), and computed tomography (c).

Magnetic resonance images showing a 2.4-cm multilocular cystic mass in the left adrenal gland from a coronal T2-weighted view (a) and a heterogeneous high signal intensity mass in the pancreatic tail from an axial gadolinium-enhanced T1-weighted view (b). A CT scan was performed 12 months after the initial visit showing the left adrenal cystic mass with peripheral rim enhancement had increased in size by 0.3 cm during follow-up (c).

tail with recurrent peptic ulcer disease (Zollinger-Ellison syndrome), hypercalcemia due to parathyroid hyperplasia, hyperprolactinemia due to prolactinoma, nonfunctional adrenal cystic mass, meningioma, and right breast carcinoma *in situ*. She was administered cabergoline and underwent laparoscopic distal pancreatectomy. This histology showed a grade 1 (pT2Nx) pancreatic neuroendocrine tumor (two lesions, 2.2cm and 0.9cm in diameter and both were synaptophysin positive and chromogranin positive). After a pancreatectomy, her gastrin level decreased to 771 pg/mL. Approximately 2 months following her distal pancreatectomy, a total parathyroidectomy with auto transplantation and a wide local excision of her right breast had been performed. After the parathyroidectomy, her total calcium level normalized to 8.6 mg/dL, phosphorus level was 4.3 mg/dL and PTH level was 7.4 pg/mL. Pathology was consistent with parathyroid gland hyperplasia. The resected breast tissue indicated ductal carcinoma *in situ* (two lesions: one 0.7×0.4cm and the other 0.6×0.4cm, with no regional lymph node metastasis) demonstrating estrogen receptor-positive, progesterone receptor-positive and HER2/neu proliferation-negative breast cancer. She was administered cabergoline (1mg twice/week), calcium carbonate (500mg thrice/day), calcitriol (0.25 µg twice/day) and tamoxifen (20 mg). Based on her age and FSH levels in the premenopausal range at the follow-up visits, as she never had a menstrual period in her entire life, tamoxifen was chosen by a breast cancer expert rather than an aromatase inhibitor,

even though her FSH levels can be modified with prolactin-secreting pituitary macroadenomas.

Following the surgery, she received radiation therapy (60Gy/30fx) at the right breast and axilla. Carbergoline treatment for 6 months decreased prolactin levels to 57 ng/mL and decreased the size of the pituitary adenoma in the sella MRI (Fig 2). After 12 months, her prolactin levels decreased to 26.8 ng/mL, but her gastrin level showed fluctuation. In the beginning, her gastrin level decreased from 1462 pg/mL to 357 pg/mL, but recently the level increased to 643 pg/mL. Therefore, we searched for other recurrent gastrinoma lesions using a Indium 111-octreotide scan and endoscopic ultrasound. These showed no evidence of abnormally increased uptake or identifiable lesion. During her follow-up, she was frequently taking proton pump inhibitors for her gastric symptoms. Her serum gastrin level increased through use of the proton pump inhibitor (9), and we are planning to follow her gastrin level regularly with appropriate imaging.

DISCUSSION

MEN1 can have various presentations including various abnormalities of the parathyroid, pancreas, anterior pituitary and/or other less common diseases (ie. adrenal cortical tumors, carcinoid tumors, lipomas, collagenomas, and meningiomas) (2). MEN1 is usually inherited in an autosomal-dominant pattern, or sporadically without any family history. The MEN1 gene is located on chromosome 11q13. Most associated

Figure 2. Sella magnetic resonance images (a) at initial visit, and (b) after cabergoline treatment.

A coronal T1-weighted gadolinium enhanced view showing the 1.5-cm mass with heterogeneous enhancement on the right side of the pituitary gland with a pituitary stalk thickening and deviation to the left at the initial visit (a), and significantly decreased size of the right pituitary mass without the disappearance of stalk deviation and thickening, 10 months after cabergoline treatment (b).

genetic abnormalities are germline mutations in the MEN1 tumor-suppressor gene, or some deletions. Some patients, who sporadically develop MEN1, may be unrecognized as having the disease or there may be a delay in diagnosis. Therefore, clinicians need to pay attention to taking a detailed family history, performing a mutation analysis, and assessing various clinical features of MEN. Our case was a pathogenic variant at chr11q13. It is an intron deletion mutation that influences gene splicing, compared to previous an exon mutation. Our case was a patient with MEN1, breast cancer, and an incidentally detected adrenal tumor. In other words, our case was the first report that showed MEN1 gene intron mutation and their clinical phenotype with MEN1 and adrenal incidentaloma.

Adrenal abnormalities associated with MEN1 have been reported since before 1960 (3), and its prevalence has been reported to be as high as 20.4% (4). Recently, adrenal incidentalomas have been detected increasingly, owing to improvements in diagnostic skills. Evaluation of this adrenal incidentaloma is generally focused on whether or not biological functions and malignancies exist, such as adrenal cortical carcinomas (ACC) (4, 10). Sporadic adrenal incidentaloma is usually non-functional and has a low risk of ACC occurrence. On the other hand, adrenal lesions associated with MEN1 may present with steroid hyper-secretion within the renin-aldosterone system and have a high risk of ACC occurrences (4). Gatta-Cherifi *et al.* studied the clinical characteristics of adrenal involvement in MEN1 patients (4). Adrenal enlargement in MEN1 patients was reported in 20.4% patients and the mean age was lesser than that of patients with adrenal incidentaloma (46.1 years vs. 55.0 years, respectively). They showed more cases of primary aldosteronism, and some revealed loss of heterozygosity for polymorphic chromosome 11 DNA markers in surgically resected adrenal tissue. The prevalence of ACC in MEN1 patients was significantly higher than in patients with adrenal incidentaloma (13.8% and 1.3%, respectively, $p < 0.05$). Furthermore, interestingly, some ACC occurred after several years of following up on small adrenal tumors.

Therefore, clinicians should focus on the relationship between adrenal incidentaloma and MEN1 including steroid secretion and the occurrence of ACC. Our patient had a non-functional, benign appearing, left adrenal mass with MEN1 that demonstrated a slight increase in size of 0.3 cm according to a CT scan performed 1 year after pancreatic surgery (Fig. 1 C). Thus, regular follow-up will include careful monitoring

of her adrenal hormones and ACC occurrence.

Some studies have reported the association between MEN1 and breast cancer (5, 12-13). In the International Breast Cancer in MEN1 study group, female patients with MEN1 were shown to have an increased risk for breast cancer (relative risk of breast cancer 2.83 $p < 0.001$). The study found that loss of menin expression and loss of heterozygosity at the MEN1 locus affected mammary-cell autonomicity (5). Previous studies suggested that MEN1 is involved in breast cancer initiation in animals (13), and implicated in breast cancer progression through its encoding of menin, a co-regulator of estrogen receptor α (14, 15). Koen *et al.* reported that MEN1 co-regulated a proliferative breast cancer-specific gene expression program in ER+ cells, compared to that MEN1 exerted an anti-proliferative function in primary mammary cells (15). Recently, Rachel *et al.* reported that MEN1 patients were experiencing early onset breast cancer (6). The mean age at breast cancer diagnosis was 40-56 years, compared with an age of 60-65 years in the general population (6). Therefore, they recommended earlier breast cancer surveillance from the age of 40 years old for women with MEN1 (6). Our patient was a 48-year-old woman who had MEN1 and an incidentally detected adrenal tumor. She had fortunately detected early breast carcinoma *in situ* in screening for MEN1. Therefore, clinical doctors need to keep in mind earlier breast cancer surveillance in patients with MEN1.

In conclusion, we reported a 48-year-old female patient who had adrenal incidentaloma diagnosed with MEN1 and breast carcinoma *in situ* with a pathogenic variant occurring within the intron at chr11q13 (MEN1 NM_000244.3:c.1365+1_1365+11 del, GTGAGGGACAG). Considering the increasing incidence of adrenal incidentaloma and 20% prevalence of adrenal tumors in patients with MEN1, it is important to rule out MEN1 associated with adrenal incidentaloma early on. Female patients with MEN1 are at increased risk for breast cancer; therefore, we should consider intensified breast cancer screening in female MEN1 patients from an earlier age than average risk women. Furthermore, patients with adrenal incidentaloma and other MEN1 associated tumors should be screened for mutations in menin.

Conflict of interest

The authors declare that they have no conflict of interest.

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